there have been a number of outcome studies now that show that for some reason that we do not understand that it was helpful.

Another reason for the folding that I think everybody needs to understand is that if you put this sort of flat device which is oval in cross-section in a pocket that then begins to contract and so that the device is now compressed into more of a sphere, it's going to fold, and I don't know any way that the manufacturer or anybody else can really prevent that.

In regard to reverse diffusion, that was brought up today. There was no evidence that I could detect that I was aware of that it was a significant problem and no evidence presented that it was a problem.

If there is diffusion of that sort, it would be through the valve, but there's no reason to believe that's significant.

Local complications. Contracture is the big problem, and everybody should understand what happens with contracture. There's a membrane that

forms around the implant and for some reason that we do not completely understand, the membrane contracts.

It often happens unilaterally. It is not a systemic response, and the most prevalent theory at the present time is that it is a low grade bacterial infection from the breast ducts, which may explain why we get better results in the retromuscular position, and it also explains the use of Betadine, which I think is one of the things that has surprised a lot of people here, because that wasn't brought up. And Betadine is used in an attempt to sterilize the pocket.

There are questions that have been brought up about the shelf life of saline. Saline per se, so far as I understand it, has an indefinite shelf life. All it is is salt water, and I think that the expiration date that has been presented here, it really refers to the container more than to the saline itself.

Fungal growth in saline, I think most of us have seen that. The situation has changed a lot since those cases were initially presented. We used

to use an open tray to fill the implants. In other words, we would pour saline to an open tray on the Mayo stand, take the saline out with a syringe, and use it to fill the implant. That was pretty much the standard of care.

I think what has happened is that there's airborne fungi, and they would get into the open tray and then be put into the implant. There's no reason to believe that that contamination comes from the patient herself, and the method of filling now that so far as I know everyone uses is a closed method of filling from an IV bag with a three-way valve, a three-way stop cock to the syringe. So I don't think that that's the issue that it once was.

Rippling is going to occur, specially in the thin breast. It's going to be seen. There's no way to get around that at the present time because the implants are going to ripple.

The information we have in our literature suggests that sensory changes in the nipple and the areolar area are related not so much to the location of the incision as to the position that the implant is

placed, whether it's behind the muscle or in front of the muscle, and I realize that that doesn't correspond with what was just presented here, but I think we need to be aware of that.

Mammography may be made more difficult without any question whether the implant is behind the muscle or whether it's behind the breast, but all of the studies we have fail to show any difference in the tumor stage when detected or in the long term survival. So so far as an outcome is concerned, it doesn't seem to be a major issue.

That's mine.

CHAIRMAN WHALEN: Thank you, Dr. Burkhardt.

Actually unless there's specific questions that we'll raise from time to time, you needn't necessarily reside at that table. We'll just ask you to come up to the podium if we do have a question to ask you.

Thank you.

For statistics, Dr. Blumenstein.

DR. BLUMENSTEIN: Well, when I thought

about this, I found myself thinking of how I would respond if the information given to me were given to me as an article to be reviewed for publication in a peer review journal, and so a lot of what I'm going to say here has to do with holding the information to that standard, but there's also the standard of trying to be informative to the potential recipient of an implant.

The theme of what I'm going to say has to do with the presentation of the data; do not take into account the censoring and, therefore, the conditional probabilistic aspect of what's going on in the presentation of the data. I'll make that a little bit clearer as we go along.

The Cox regression analysis, Cox proportional hazard regression analysis looks like it's somewhat useful. However, I would point out that that would be very difficult for the consumer or physicians to understand.

Also, for someone who wants to talk to me later, I would have some ideas about how time dependent covariance might be brought into that

analysis in order to improve some of the precision of the analysis.

However, I want to go on and talk about the data itself, that doing Cox proportional hazard regression on data that's kind of smelly might not be the best thing in the world.

I want to talk about several methodologic issues that are more technical in nature, and the first thing I want to say is, of course, and as has been pointed out before, these studies are not randomized clinical trials. They don't come even close to that, not to propose that anybody could do a randomized clinical trial, but just in terms of weighting the evidence we don't have that kind of evidence here. We don't even have control groups, and so these data should be very carefully interpreted.

Some of the plots that were presented and some of the language that was used tried to represent the individual risks as cumulative incidents. That's absolutely wrong. They are not cumulative instances. One minus a Kaplan-Meier curve is not a cumulative incidence curve. That is a cumulative conditional

probability curve. I have some references if someone wants to look at them. We must have these things labeled correctly to the patient.

I would suggest that you do look at real cumulative incidence methodology as a means of presenting the risk data and those same references would address that.

The issue of interval censoring has been brought up before. I'm not sure what to do about that. That's a difficult problem here. I suspect it's a matter of simply pointing it out in the publication as a source of bias, as has been previously discussed.

One of the very difficult issues that's here is that the confidence intervals that are presented are confidence intervals that represent the experience of a group of patients and do not represent the uncertainty of the estimates that pertain to an individual patient's risk. This is a problem that exists everywhere wherever risks are trying to be presented. It's a difficult problem, and I don't have an answer for it other than in certain specific

situations.

Now, there's a number of data issues, and all of them are related to what I call informative censoring, and I think it's absolutely wrong that the data have been presented here without any analyses to show the characteristic, to try to characterize the patients who are not followed for specific time points.

There is information that the types of patients who are dropped out over time could be biasing the data significantly. You could be comparing demographics. You could be comparing whatever reasons for dropout you might have. You could be comparing baseline assessments in terms of some of the measures of quality of life or some of the mechanical measurements and so forth.

So essentially what I'm saying is you can compare the baseline data between patients who are included in an analysis for a subsequent point in time to the patients who are not included. It's just a very minimalist approach to trying to get a handle on whether the data from patients who are not included in

subsequent time points are different from the data that are there.

This kind of informative censoring applies to the efficacy data, the quality of life data, and the risk data. It applies to everything in this kind of study.

Dr. Bandeen-Roche pointed out that especially in the quality of life data the patients who were explanted are not represented in the subsequent, the late time point analyses of these data. This is an extreme limitation and misrepresents the data unless you point it out and very carefully document that that's exactly what you're doing.

It's wrong to represent that as being an unconditional quality of life assessment.

The follow-up for the data here are just too short, and I will, I'm sure, talk about that later. In short, my take on all of this is that I cannot accept the accuracy of any of the data here because of the limitations that I'm pointing out. It may be that we do have some rough idea, some very crude idea of the relative size of these risks and

ranking of the risks, but I cannot feel good about any of the data presented with respect to accuracy and giving that information to an individual patient and having that patient understand what the real risks are.

CHAIRMAN WHALEN: Thank you.

With apologies for twice having put you off, Ms. Domecus, if you have a question.

MS. DOMECUS: I just want to go back to Dr. Li's criticisms regarding the mechanical testing study design. As I understand it, it seemed like he thought there was a disconnect between the laboratory testing study design and how that could mimic what was seen clinically, and I was just wondering if you had any suggestions on how those tests could be designed at this point or maybe later, but I think that might be helpful to the manufacturer since, as you suggest, they've done an awful lot of testing, put a lot of effort in, and if it doesn't kind of hit the mark for you, if you had some suggestions, I thought that would be helpful.

DR. LI: Well, I suppose I do, but it

probably would take a long time. We'd have to sit down for a long time and work that out, but I think one suggestion that I could definitely make though is to continue the type of retrieval analysis that they've begun to do because I think that is going to be the proof in the pudding.

In other words, in other devices that I work on, the whole purpose of our laboratory is to try to develop an in vitro test that where at the end of it it looks like the failed device, and the closer you can get to that, the better off you are in developing an apparatus or a test that would say, "Look. If I improve the properties this way, I can measure it and it will be better or worse clinically than what I've got."

So in the absence of knowing the exact mechanism for the failure, I'm not exactly sure what test to suggest.

CHAIRMAN WHALEN: Did you also have a question from earlier of the sponsor that --

MS. DOMECUS: It got answered.

CHAIRMAN WHALEN: Thank you.

Do any of the other panel members have any questions first of the sponsor before we go on to attempt to answer the FDA questions?

DR. BURKHARDT: I have one more question for the sponsor. When these failures occur, Mr. Purkait, don't they usually occur at the end of a fold?

MR. PURKAIT: Sometimes they do.

DR. BURKHARDT: Sometimes?

MR. PURKAIT: Yes.

DR. BURKHARDT: But not consistently?

MR. PURKAIT: Not consistently.

DR. BURKHARDT: Thank you.

CHAIRMAN WHALEN: Dr. Chang.

DR. CHANG: Also, was there any relationship between thickness of the implant and sell failure? Was that ever measured or considered?

There's a variability in the thickness of the models or range of thickness?

MR. PURKAIT: Yeah, we have range of thickness for the smooth and the SILTEX, which is textured. We have information that shows that

regardless, within the same model type, whether it's the smooth or SILTEX, within the same specification any of those tests show the same results. So thickness does not cause problem.

DR. BOYKIN: Could I ask one more question while you're there?

A comment in the summary, and I don't think we've really talked about this, is that within one device there could be a variation of almost the entire thickness at the thinnest point of the shell, like from 17/1000 to 34 or 35/1000 of an inch; is that correct?

MR. PURKAIT: That's correct.

DR. BOYKIN: Now, this reflects the inherent difficulty in fabrication of the device, that you can't control the tolerance of the limits any closer than that?

MR. PURKAIT: To some extent that's exactly true. The way the shell works is that these are all done by the dipping process, and if you take a particular viscous material and if you dip the mandrel, and if you turn it over, normally those

things tend to drip down there. So you get a variable thickness from the top to the bottom. That's why you see the 14,000 to 38,000 is the difference.

But I just wanted to point out that most of our test data though we target for the area of the thinnest possible shell.

CHAIRMAN WHALEN: Dr. Morykwas.

DR. MORYKWAS: I just had a thing where you commented on the white line on the implant is interesting, and if you could, with the repeated folding have you analyzed any of those where the white line is for the induction of crystallization or crazing or anything in the polymer material itself that might change some accountable properties?

MR. PURKAIT: We did previously some of those. We have looked into some of the explants. One thing I just want to bring to the attention that explant is very difficult because by the time we get the explant, this particular explant has been altered a few times because they go through sterilization; they go through the wash process; they go through various different handling procedures.

Therefore, by the time we really actually do that, we probably have not seen everything that's coming out of the body. Nevertheless, we do try to characterize as best as we can.

To answer your questions, we did not see per se any creasing effect or super crystallization on those areas because of the stress there.

CHAIRMAN WHALEN: Thank you.

Are there any questions of any of the panel members for any of the three FDA presenters?

(No response.)

CHAIRMAN WHALEN: Seeing none, we will being to attempt to answer FDA's questions.

Dr. Berkowitz, would it be possible to re-project those questions sequentially as we try to deal with them?

And for --

PARTICIPANT: (Inaudible.)

CHAIRMAN WHALEN: You will have a comment period, sir, shortly.

On many of these questions I will poll the entire panel. On come I will be somewhat more

focused, and the first question which we see projected is one of these more focused ones that Dr. Li is our subject matter expert on, and we'll begin with him.

DR. LI: Well, in general, I think the fatigue testing and fold flaw testing are incomplete in that they either did not test all the models and/or did not test the final materials that ended up in the commercial device, the last issue being the reference to switch to the Sytech silicone from the original PTC, which is the bulk of their data. So it is at best incomplete.

The fatigue testing and the fold flaw testing I do not believe provide any long term information to us to the rupture and leakage of the implants. I think looking at their data, I would have no way to predict when they switch, for instance, from the PTC to the Sytech whether or not the rupture leakage rate will be the same, better or worse. So I guess my comment on the sponsor's methodology and results is that the methodology, although it represents some construct testing -- oh, actually one important thing. Correct me if I'm wrong, but most of

your fatigue and rupture data did not have the valve in the implant; is that correct?

PARTICIPANT: We did have the valve.

DR. LI: They did have the valve. Okay. Fine.

So in general I think the methodology, although presents some device testing, I don't think any of it is reflective of what we could expect to happen in the patient. So I think what they've got unfortunately is a little incomplete, and I don't know what to do with the information as far as projecting what the long term rupture and leakage of the implants will be.

CHAIRMAN WHALEN: So in regard to our first question on this testing, are there other members of the panel that would like to address that?

Just to remind everyone on the panel and in the audience, the way this will proceed is that when the panel has attempted to answer the question, I will then attempt to summarize, although there was only one responder in this case, to Dr. Witten on behalf of the FDA what the panel's answer is, and then

if Dr. Witten finds that a satisfactory answer, we'll proceed to the next question.

Dr. Witten, in regard to question number one, it is the panel's opinion that at best we are given incomplete testing, and that specifically in regard to fatigue and fold flaw testing, that while the methodology and the results were exposed to us, that there seems to be little or no correlation with the long term clinical actualities that are witnessed.

Is that sufficient for your answer?

DR. WITTEN: Yes. Thank you.

CHAIRMAN WHALEN: Thank you.

If we can go to question number two on the projection screen, this is one of the questions that I will ask that everyone comment upon the question, and this has to do with the issue for patients who are receiving the implants for augmentation.

Given what has been presented to us by the sponsor, do we find in accord with the federal regulations that the product is both safe and effective for augmentation patients?

I will begin going around with Dr. Chang.

DR. CHANG: Certainly the analysis presented by Dr. Anderson gives credence to the fact that with respect to change in size and for some of the parameters of quality of life that the device is effective for augmentation patients.

I want to qualify my comments about safe, safe with qualifications, in that several of the complications listed, and in fact, the high number of complications listed is not in the purview of the manufacturer; that it is dependent on the practice of the physician. So it's a very qualified safe product.

And the remaining question in my mind is that 5.8 percent deflation/leakage rate.

So for effectiveness, yes, in augmentation; for safe, a qualified yes, given parameter that are actually in the control of physician, not the manufacturer.

CHAIRMAN WHALEN: Thank you.

Dr. Morykwas.

DR. WITTEN: Excuse me. Can I clarify before you go around the room? Yes?

The way that 21 CFR 860.7, we're asking

you actually about reasonable assurance of safety and effectiveness. So it's not an absolute safe and effective. The definition is reasonable assurance of safety and effectiveness.

CHAIRMAN WHALEN: Thank you.

DR. MORYKWAS: I would just like to also agree that I think the product has been shown to be effective, and I will just somewhat parrot some of the conclusions of Dr. Chang, that several of, I think, the safety issues aren't really the responsibility of the device itself. It is more the physician or the physicians who are implanting it. So there are concerns there.

And some of that, I guess, is out of our purview. I don't think we can legislate how the surgeon will do that.

But still with -- well, again, I'll get back to Dr. Li also -- his comments that it is relatively safe, yes, but still there is a high degree of deflation that doesn't seem to gibe with in vitro data.

CHAIRMAN WHALEN: Thank you.

Ms. Dubler.

MS. DUBLER: I do think the effectiveness, which is largely measured by the response and satisfaction rates of the patients themselves, is impressive and provides reasonable assurance that it is effective.

I'm troubled by the combination of factors that are either under the control of the manufacturer or part of the practice patterns of surgeons or, in the third place, part of the body's reaction to these devices, and it's hard for me to sort them out.

I'm not sure I agree that we can't legislative how surgeons go. I don't think we can legislate it, but I think the notion of best practice is a very powerful one, and I think that if there are better ways to use these devices, that has to be very, very clear in how they're marketed and who uses them and under what conditions.

But I am concerned about the 5.8 deflation rate and by the reported 43 percent complication rate and 73 percent complication rate in reconstructive patients. I think that's very, very high, and the

combination of all of that makes we reluctant to say that we can provide reasonable assurance that, in fact, they're safe.

CHAIRMAN WHALEN: Dr. Robinson?

DR. ROBINSON: I believe that the product is effective, with the word "reasonably," "reasonably safe," I'm worried that no matter what type of ex vivo testing we suggest, there won't be a link between that testing and prediction of what happens clinically. So we may be getting into a situation where we're looking at more and more ex vivo testing and still coming back and asking the question what does it mean clinically.

But the use of the word "reasonably" is fine with me. It's reasonably safe.

CHAIRMAN WHALEN: Thank you.

Ms. Brinkman.

MS. BRINKMAN: Well, in regard to effectiveness, obvious it's perceptual. It's true then that deflation can't be considered effectiveness because I would think if I had an implant and it deflated I would not think it was very effective.

But anyhow, as far as safety goes, I think

it's appalling that for an elective procedure for augmentation that there is 43 percent, first complication rate of 43 percent, and it continues. I mean, it never levels off. It continues to grow.

And so I guess I feel negatively about the safety of the product, even though I know that there are many women who want them, and I think the manufacturer does what they can.

CHAIRMAN WHALEN: Ms. Domecus.

MS. DOMECUS: I think effectiveness has clearly been shown. I guess when I look at the individual adverse event rates they all look reasonable, but the 43 percent number does seem high, especially for a cosmetic indication, and in my experience I don't know that I've ever seen a medically indicated product have that high of a complication rate and have it be a favorable risk-benefit ratio. So that would be concerning to me.

CHAIRMAN WHALEN: Dr. Li.

DR. LI: I agree with everyone on the effectiveness of the implant.

I think the reasonably safe part, I think,

would come down to whether or not you believe 5.8 material or design failure of the device is a reasonable level. I think for my own purposes, for the short length of time these devices were followed, that's an alarmingly high what I'll characterize as the design and material failure, and although the surgeon may have a large input on this, and I never intend to legislative surgical behavior and skill, I think part of what we are able to do is either to design or test for the variations that one would expect a physician to apply in the implantation of this device, and I don't believe that particular range of possible surgical procedures has been explored.

So I would say although I would say it's effective, I would have to come that it was unreasonable for safeness.

CHAIRMAN WHALEN: Thank you.

Dr. Blumenstein.

DR. BLUMENSTEIN: I agree that it appears that there's some efficacy here in terms of the intended purpose of augmentation. I think the safety issue is largely dependent on how well the risks could

be communicated to the potential recipient of one of these implants.

And I think accuracy has part of that, and so forth. I think the best overall representation to the potential recipient is the time to first bad thing, which has been already characterized here as being the best measure.

CHAIRMAN WHALEN: Dr. Boykin.

DR. BOYKIN: I would agree that we have evidence that the device is effective, and I would like to underscore the comments concerning the environment that this whole process is taking place in.

This operation is an invasive surgical procedure, and it is associated with an inherently dynamic process that occurs around this static, inanimate object, and this is also affected by the patient's own chemistry in terms of how they heal, the drugs they're taking, whether or not they smoke cigarettes, where they live, and how they live their lives.

These are generally considered the

surgeon's complications, if you will, and not necessarily the device's.

We've seen a disparity between the mechanical testing and the clinical evidence of failure which to me just basically means we need to go back and redesign some tests.

Overall, however, I believe what we can say about the safety is that we understand probably better than ever before what these factors are, what the patient will be faced with, but that to a fairly great degree, I believe that a lot of these complications are away from the domain of the device itself, and I think that it is reasonably safe.

CHAIRMAN WHALEN: Thank you.

Dr. Bandeen-Roche.

DR. BANDEEN-ROCHE: Let me just first say this is an appropriate time for me to read into the record that I'm not a regular member of this panel, that I was asked to serve on this panel because I'm very highly qualified to evaluate the strength of epidemiologic evidence and had a substantial experience with self-reported health function and

quality of life data, but not because I have particular specialty in plastic surgery or implants.

That having been said, in terms of safety, my reading of the epidemiologic evidence in its total is that the devices are reasonably safe, if safety is defined as a very hazardous event, such as death, systemic diseases, that sort of thing.

In terms of effectiveness, I believe that the device has been shown to satisfy rather narrow definition of effectiveness, that is, increasing of bust size, some evidence of increase in body image. I did not find any strong evidence for increases in self-esteem.

Quality of life was not really assessed, and I agree with Ms. Brinkman in that in my mind efficacy also has to do with complications, you know, reoperations, cosmetic complications that occur at a high enough rate that I don't feel that I can give a blanket reasonable assurance in terms of high probability of a desired outcome and, therefore, effectiveness.

CHAIRMAN WHALEN: Dr. Burkhardt.

DR. BURKHARDT: I believe the safety in surgery is always qualified. It always comes with qualifications, and this particular operation is no exception.

My comments about physician behavior and the probability of being able to change that through the mechanism of this particular agency are perhaps colored by my knowledge of how training works and the fact, and probably most people are unaware of this.

Once you are licensed in a state as a physician, you are legally entitled to do any operation that you can do, provided you do it in your own environment, in your office or whatever. There are no restrictions legally regarding what any physician may do with any particular patient, and we're in a situation now where we're seeing more and more of this with people who are not plastic surgeons or who define themselves as plastic surgeons but don't meet the usual qualifications are doing this kind of surgery.

And all I'm saying is that that's going to be very difficult to control through this agency or by

any action of this committee.

I believe that the --

CHAIRMAN WHALEN: Excuse me, Dr. Burkhardt. Dr. Witten was just addressing this.

DR. WITTEN: Yeah, I think we want to focus on for this product.

DR. BURKHARDT: I understand that. I understand that, but that was brought up, and I felt that I should respond to it.

I think that so far as I can see these have been proven to be effective, and I think they're reasonably safe.

CHAIRMAN WHALEN: Thank you.

Dr. Witten, in regards to patients receiving this device for augmentation purposes, in attempting to answer whether or not we the panel deem it to be reasonably safe and effective, I believe there is near unanimous opinion that it is effective within the important constraints of defining effectiveness as we have viewed it today, but there is less than consensus on the issue of safety inasmuch as nearly everyone on the panel is significantly troubled

by the complication rates that have been reported by the sponsor, but there are various interpretations upon the significance of those complication rates inasmuch as they relate to the definition of safety.

Does that answer your question?

DR. WITTEN: Yes. Thank you.

CHAIRMAN WHALEN: We go on to the third question which has to do with the same issues of reasonable safety and effectiveness, but this time as regards those patients who receive this implant for reconstructive purposes, and we'll skip over and begin with Dr. Morykwas.

DR. MORYKWAS: Well, again, I think that we can or at least in my opinion the device has proved to be effective, and then coming to the issue of safety, the complication rate does increase significantly for this patient population, but some of that is to be expected just due to the nature of the patient and their systemic conditions which has caused them to need to be reconstructed.

But I would believe that this device would be reasonably safe even with the higher complication

rate.

CHAIRMAN WHALEN: Thank you.

And I would just interject before Ms. Dubler gives us her answer everything that was said the last time was insightful and important, and I'm not reflecting upon anything anybody said, but if you just simply agree with what you said the last time, it's perfectly acceptable to say, "I feel the same as I did last time."

Sorry.

MS. DUBLER: Actually I think there's another factor when reconstruction is at play, and for me, as I think the choice for a woman is different under those circumstances, I would wonder what her options would be. In other words, if all of the options for the prosthetic devices have the same complication rate, I might still say that for a woman facing reconstruction that that might be safe enough under those circumstances.

Aside form that, I ditto what I said before.

CHAIRMAN WHALEN: Thank you.

Dr. Robinson.

DR. ROBINSON: Ditto what I said before.

CHAIRMAN WHALEN: I may have started a trend.

Ms. Brinkman.

MS. BRINKMAN: Unfortunately I cannot do a ditto.

I think this becomes even a much more devastating issue for me. Unfortunately we just haven't studied a large enough number of patients for me to agree that it's safe and effective.

CHAIRMAN WHALEN: Thank you.

Ms. Domecus.

MS. DOMECUS: Again, going back to the risk-benefit ratio, I would feel comfortable saying that for this indication that safety and effectiveness have reasonably been shown. Even though the risks are higher, I think there's a unique benefit here, and the risk-benefit ratio, I think, is favorable for this patient population.

CHAIRMAN WHALEN: Thank you.

Dr. Li.

DR. LI: Same answer as before.

CHAIRMAN WHALEN: Thank you.

Dr. Blumenstein.

DR. BLUMENSTEIN: I would like to put just one qualification on the answer here. It really applies to what I said before as well as this, and that is that I want to make sure that the characterization of effectiveness provides adequate data on quality of life benefits appropriately analyzed, and so forth.

CHAIRMAN WHALEN: Thank you.

Dr. Boykin.

DR. BOYKIN: No change.

CHAIRMAN WHALEN: Thank you.

DR. BANDEEN-ROCHE: My comments on safety and complications are unchanged.

With regard to the quality of life, I think it's even a more narrow definition of effectiveness in this case. No evidence that the implant affected quality of life and not just recovery from surgery, other than anecdotal evidence.

Thank you.

CHAIRMAN WHALEN: Dr. Burkhardt.

DR. BURKHARDT: Effective and reasonably safe.

CHAIRMAN WHALEN: Thank you.

Dr. Chang.

DR. CHANG: Effective and reasonably safe.

CHAIRMAN WHALEN: Thank you.

Dr. Witten, in regards to patients who receive this device for reconstruction as regards reasonably safe and effective, generally the same opinion that was voiced to you in the prior question is reflected with perhaps two important exceptions, and that is that the effectiveness as regards the frame of reference of indications is different in this particular subset of patients by virtue of what options the patients may have, and that the single subject matter expert with the best expertise as regards quality of life type of data feels that that has not been sufficiently answered by the sponsor's presentation.

Does that answer your question?

DR. WITTEN: Yes. Thank you.

CHAIRMAN WHALEN: Thank you.

We proceed to question number four. With the exception of the one year follow-up data in the implants and the FBS study, FDA asserts that the sponsor has not collected safety and effectiveness information for the cohort of revision patients, and yet the sponsor is proposing revision as an indication for use.

Since this is about 30 percent of patients who present for this operation, we are asked to discuss whether sufficient safety and effectiveness data, to include revision, as in a mentioned stated indication and whether the sponsor should evaluate the safety and effectiveness for revision patients as a condition of approval. Please also comment on the information that would be useful to collect in a post approval study.

Ms. Dubler.

MS. DUBLER: I find this a very hard question because it builds on the uncertainties of the two that preceded it. Given my lack of comfort with the first three questions, I would request that the

sponsor investigate revision in a more detailed fashion, although it's beyond my capacity to make specific suggestions.

But I think before they could include revision, they would need to collect more data and be very certain what their measures were.

CHAIRMAN WHALEN: Thank you.

Dr. Robinson.

DR. ROBINSON: Since I believe it's a reasonably effective device, I think revision should continue as an indication and perhaps some discussion could be on a post approval continuing to collect data in this particular group of patients.

CHAIRMAN WHALEN: Thank you.

Ms. Brinkman.

MS. BRINKMAN: I believe there's a lack of safety and follow-up data.

CHAIRMAN WHALEN: Ms. Domecus.

MS. DOMECUS: Again, is revision here meaning revision for any reason, not just for cosmetic reasons?

CHAIRMAN WHALEN: Well, inasmuch as we're

really sort of focusing it upon a labeling application here and since the word revision is there and not necessarily with qualification.

MS. DOMECUS: I would think we wouldn't want to preclude patients from undergoing a revision procedure if they wanted to, especially if they're doing it for a complication. So even if there isn't as much data as we'd like to see in it, I think that it should be part of the approval, where many issues can be done post approval.

CHAIRMAN WHALEN: Maybe I would ask Dr. Witten if a little clarification here would be in order. If we don't mention revision in the indications, that would not in and of itself preclude a patient receiving this device for revision. However, it would more focus what the standard set of indications for using this device would be. Am I correct in saying that?

DR. WITTEN: That's correct.

CHAIRMAN WHALEN: Dr. Li.

DR. LI: Yeah, with that clarification I'll say there's not enough information to accept it

for safety as revision. The thing that sets me off a little bit on that is that it's a little bit surprising and somewhat unexplained why in the reconstruction case the deflation rate is so much higher, and now we have a revision series in which we have no information hardly at all.

It's unclear how you would predict what that would be. So I think I would definitely ask for a follow-up.

CHAIRMAN WHALEN: Thank you.

Dr. Blumenstein.

DR. BLUMENSTEIN: Well, I feel like that the patients who are undergoing revision will be a lot more informed than the patients who are undergoing their first implantation. And so with that condition, I feel that there's a little bit less of a concern about informing patients, although other things can happen besides what happened the first time.

So I feel that more data need to be collected, but I would go along with the indication.

CHAIRMAN WHALEN: Thank you.

Dr. Boykin.

DR. BOYKIN: I believe clinically speaking this indication really falls in between the two areas that we've looked at. It should, I believe, at least from my experience, be considered a continuum of the spectrum.

While there is relative paucity of data, I believe that this could be continued as a post approval study and that the complications that have been investigated should continue to be documented.

CHAIRMAN WHALEN: Thank you.

Dr. Bandeen-Roche.

DR. BANDEEN-ROCHE: While I agree that the data collection needs to continue hopefully along many of the same parameters that have already been collected, it is very conceivable to me that medical and biological and mechanical analogy would be sufficient to approve this for revision if we're approving it for the other things, and I would defer to the other subject area experts on that.

CHAIRMAN WHALEN: Dr. Burkhardt.

DR. BURKHARDT: That's such a fuzzy question I still can't understand it. I cannot

imagine a situation in which you would have a patient who has had a safety and effective implantation primarily, needs a revision, and then say, "Well, it was okay for the first time, but not for the second time."

And I can't imagine that an implant that would be judged safe and effective for an initial procedure would not be judged safe and effective for a revision procedure, and I believe it should be included as safe and effective.

CHAIRMAN WHALEN: Thank you.

Dr. Chang.

DR. CHANG: I'll be consistent and leave it on as an indication and ask for post marketing study, follow-up.

CHAIRMAN WHALEN: Thank you.

Dr. Morykwas.

DR. MORYKWAS: I'll also agree that it should be approved with post market approval because you also could run into the situation where a woman with bilateral implants has a unilateral explantation and then couldn't be revised, and that's a peculiar

conundrum that would be in there.

So I would recommend a yes.

CHAIRMAN WHALEN: Thank you.

Dr. Witten, there is not a unanimity of opinion on this particular subject. However, it is, I think, the clear preponderance of the panel's opinion that there should be a directive for further data to be collected upon this issue of patients who receive this device for revision.

On whether or not this should be a part of the labeling, there is pretty much a division 50-50 of opinion on this particular topic.

DR. WITTEN: Thank you.

CHAIRMAN WHALEN: Thank you.

Going to question number five, this is sort of a side point of what we were talking about a little bit earlier in terms of the complications, but it focuses upon long term adverse events, and I would ask that those in responding address the three lettered subpoints of question number five, and we, I believe, start with Dr. Robinson.

DR. ROBINSON: The increasing rates per

year for a device, I mean, devices over time have increasing rates of complications, I think, for most. So I'm not too surprised there are increasing rates.

The minimal duration of follow-up to look at them, I think I would have to defer to the statisticians. I'm not sure I have even a gut feeling for what that should be in terms of a number.

The type of visit, I'd have to ask for some clarification. Active versus passive, what exactly is meant by that?

Pardon?

DR. WITTEN: Do you want clarification from us or --

DR. ROBINSON: Yeah, please.

DR. WITTEN: Yeah, meaning does the patient come in for, you know, to be seen. Is it a postcard follow-up? Is it a visit with the physician?

DR. ROBINSON: So active would be they're physically present.

DR. WITTEN: Yeah. In other words, what mechanism? You know, there's a range of ways of getting information from follow-up.

DR. ROBINSON: If you're going to continue to do long term follow-up, you should od it in a serious manner, and it should be active.

And which types of complication should be addressed? They should be serious complications, complications like connective tissue diseases, and things like that that I think have been laid to rest by multiple studies should not be included on these serious complications.

CHAIRMAN WHALEN: Thank you.

Ms. Brinkman.

MS. BRINKMAN: Well, I believe that the FDA in '95 asked for a minimum of ten years for patient follow-up, at least for deflation, and so certainly a minimum of ten years, although I am not a statistician. So that's my only off the top of my head, non-expert opinion.

Certainly an active visit would be preferred, but I'm not sure I believe that's realistic, and so in light of not being able to get that, then some sort of at least survey or by mail thing or the best that someone can get.

Obviously what types of complications, capsular contraction, infection, deflation, breast nipple sensation, leakage, rupture, reoperation, the whole list of complications that we've discussed to this point.

CHAIRMAN WHALEN: Thank you.

Ms. Domecus.

MS. DOMECUS: Again, I'm not sure if this question refers to preapproval or just any data that's there.

CHAIRMAN WHALEN: Actually you can phrase your answer in whichever way you desire.

MS. DOMECUS: From a preapproval standpoint I think the sponsor has more than met the typical standards for what would be required prior to FDA approval. So that any of this data I think should be a post approval setting.

The ten year stipulation that's already present, I think, is very stringent already. So I think that should not be extended.

Active or passive? I think either is probably a fine way to collect the data. In terms of

wish complications, I think all complications should be followed for the duration of the study.

CHAIRMAN WHALEN: Thank you.

Dr. Li.

DR. LI: I guess I would leave, again, the minimal follow-up to the statisticians, although the, again, short term performance of these things as far as deflation goes, to me I still consider to be quite high, but I certainly would like to follow that up for a little longer, at least the ten year suggested FDA.

I'd like the follow-up to be active. I think if we could include perhaps so that it would be a little easier to ascertain after the fact if there is a deflation or some mechanical failure that there would be some easy way to ascertain the model, the sterilization method, or the details of that particular device, and then we could answer the question is there a material and design correlation or is there not with this, and try to answer that question once and for all.

And maybe this is outside the purview of a survey, but I certainly would encourage either the

companies or some academic institution to embark on what other implant devices do and have retrieval collections and analysis because I think in the absence of that we're never going to get to the actual factual answer that will make us all happy.

CHAIRMAN WHALEN: The drum roll for the first of our statisticians, Dr. Blumenstein.

(Laughter.)

DR. BLUMENSTEIN: So I've been set up here. I have to say the number of years, huh? No way.

I think a long term follow-up, active follow-up would be very useful here for the reasons just cited, and in particular to address this issue of informative censoring, you need to know why patients are not coming back for their follow-up visits and whether that has something related to do with failures or particular types of failures.

So I think that an active long term follow-up study until that Kaplan-Meier curve starts to flatten out a little bit.

CHAIRMAN WHALEN: Thank you.

Dr. Boykin.

DR. BOYKIN: I believe the ten year period is a reasonable minimum requirement, and that if at all possible, if at all reasonably possible, the patient should be enrolled in an active follow-up phase and that the complications that we have looked at, capsular contracture, infections, asymmetry, breast feeding complications, nipple sensation, recent review of the mammography I think would also be important and maybe review of the trauma and illnesses that have occurred while the patients had the implants as well.

CHAIRMAN WHALEN: Thank you.

Another statistical opinion, Dr. Bandeen-Roche.

DR. BANDEEN-ROCHE: Well, I would like to punt a little bit and say that in my opinion statistics can't answer the question about duration if this is more than establishing the precision. If it were then we could determine number of events and do a power calculation, but it's a matter of establishing the natural history of the device. So

that's medicine and lots of things other than the statistics.

That having been said, I agree with Dr. Blumenstein's recommendation.

CHAIRMAN WHALEN: Thank you.

Dr. Burkhardt.

DR. BURKHARDT: I think that the present study has an adequate follow-up and adequate follow-up for pre-market approval. I would agree that it might be nice to get a ten year active follow-up, but pragmatically it's not going to happen, and you will be very lucky if you get a ten year passive follow-up on a significant percentage of these patients.

This is a highly mobile population, and unless you have data like they do in Canada where you can trace these people by their Social Security numbers or whatever, you're not going to get them back for follow-up for ten years.

CHAIRMAN WHALEN: Dr. Chang.

DR. CHANG: I would agree with Dr. Burkhardt's comments that it would be important to get data regarding deflation rates, but it is not

practical to expect an active follow-up, and we should not not get the data and record it because of someone having a passive -- passively giving us this information.

CHAIRMAN WHALEN: Thank you.

Dr. Morykwas.

DR. MORYKWAS: I'll just also agree that I think in the real world a ten year active follow-up is not possible and even passive follow-up in the last five years from years six to ten is doubtful, but I would agree with the other -- with (c) for all complications.

CHAIRMAN WHALEN: Thank you.

Ms. Dubler.

MS. DUBLER: Ideally an active follow-up for ten years. If that isn't possible, a passive follow-up for ten years, and in any event, I think we should track as many complications as we can in that period of time, and with a special focus on the leakage and deflation.

CHAIRMAN WHALEN: Thank you.

Dr. Witten, the panel in attempting to

answer these questions feels that with the consensus, the ideal follow-up should be active and ten years-plus, which is really in line with what FDA has already required and/or suggested, but an asterisk perhaps on that should be that some seasoned cynicism or realism, depending upon how you want to put it, thinks that that may or may not be achievable.

And that finally, in terms of complications, clearly all of those complications that we have rather extensively discussed already today should be tracked inasmuch as they have not plateaued over the period of observation, and any and all other serious complications should be as well.

Does that answer the question?

DR. WITTEN: Thank you.

CHAIRMAN WHALEN: Thank you.

Going to question number six, in regard to design of the study of the sponsor in providing information on certain long term issues, we are asked to comment, and I would specifically point out that this is as a condition of approval, although if there is some further editorialization that any of the panel

wish to make about post approval, then please do so.

And those three issues, as you see posted and before you, have to do with interference of the ability of screening mammography to detect tumors when implants are present, interference with lactation and effects of offspring from women with implants.

And I believe, Ms. Brinkman, you're up.

MS. BRINKMAN: I think these issues are going to take good education and information. Certainly that physicians, radiology techs, mammography techs, and patients need to know the importance of good clinical breast exams, that when compression techniques are available, MRIs aren't practical; that according to Dr. Berg, that we're going to see double in radiation costs and doubles in radiation doses; that people need to know where the placement of the implants are and how that affects the mammogram; that implants can hide breast tissue; that certainly the viewing may be limited by contractures and difficult to visualize.

And I think all of those issues need to be made available in provider patient information and

education.

CHAIRMAN WHALEN: Just in follow-up though, should there be anything specifically as a condition of approval or prior to approval in any of those things that you feel needs to be done?

MS. BRINKMAN: Other than those are included in our information and education in the labeling.

CHAIRMAN WHALEN: Okay. Thank you.

MS. BRINKMAN: Are we going to address lactation or are we going to just do these one at a time?

CHAIRMAN WHALEN: All three. Yes, please address all three.

MS. BRINKMAN: Okay. The same for lactation, that the ability to nurse a child may be certainly affected by having an implant, and the effects on offspring from women with implants, I don't know that there's any data out there that says that it affects babies born of mothers that had implants.

CHAIRMAN WHALEN: Thank you.

Ms. Domecus.

MS. DOMECUS: I'm not sure that I'm qualified to design the studies to address these, but I did have a couple of comments.

I think question number one about this interference with mammography, I think that it was Dr. Berg presented data on that. So I think that that's probably been sufficiently addressed, and that the sponsor shouldn't have to do that post approval.

The IOM report addresses interference with lactation and addresses that positively. So that seems like an issue that doesn't need to be further addressed.

The only comment that I'd make on that though is that one of the presenters in the open public section this morning talked about how it could actually reduce the amount of milk even if it didn't put contamination into the milk, and that's something that maybe a nursing mother, if she didn't ever use a breast pump, would not be aware of. The baby could not be gaining weight, and you could have some, you know, failure to thrive issues.

So maybe I think it's an informed consent

issue that nursing mothers need to realize their milk volume may be less if, in fact, the presenter earlier this morning was factual in his statements.

And as far as effects on offspring from women with implants, the IOM suggests that that is something that should be further studied.

CHAIRMAN WHALEN: Thank you.

Dr. Li.

DR. LI: I'll defer to my more learned colleagues on this.

CHAIRMAN WHALEN: Thank you.

Dr. Blumenstein.

DR. BLUMENSTEIN: I've been waiting for a place to say this all day, and I've finally figured it out. I think that these are very important issues and are very difficult issues to address in any kind of study or surveillance system.

Just as an idea, maybe insurance providers or managed care might have data that would be obtainable that would address these issues, and I would encourage the FDA and the sponsor to investigate those as possible sources of data addressing these

issues.

CHAIRMAN WHALEN: Thank you.

Dr. Boykin.

DR. BOYKIN: I agree that it would be important to continue to collect information. I think the IOM studies, study, rather, has given us some comfort at least in terms of the problems related to mammography and the interference with lactation.

And I think that an informed consent process could be developed by the manufacturer and perhaps reviewed by the FDA as a way to take care of this.

CHAIRMAN WHALEN: Thank you.

Dr. Bandeen-Roche.

DR. BANDEEN-ROCHE: I don't believe that the current study is well designed to rigorously investigate any of these issues. I certainly support collecting data in long term follow-up. You know about events that occur, but I would not say that further rigorous investigation is a condition for approval.

CHAIRMAN WHALEN: Dr. Burkhardt.

DR. BURKHARDT: I believe that we have all the information we need for pre-market approval.

CHAIRMAN WHALEN: Thank you.

Dr. Chang.

DR. CHANG: I don't believe any further study is required regarding these questions before approval.

CHAIRMAN WHALEN: Thank you.

Dr. Morykwas.

DR. MORYKWAS: I also don't believe any other information is required.

CHAIRMAN WHALEN: Ms. Dubler.

MS. DUBLER: I don't think the information is required before approval, were all other problems solved, but I think these three areas should be flagged to women as areas of some complexity and uncertainty, and that long term follow-up studies should be encouraged.

CHAIRMAN WHALEN: Thank you.

Dr. Robinson.

DR. ROBINSON: As I understand the question, the sponsor to evaluate these issues as a

condition of approval, so the answer to two and three would be, no, we have adequate data on that. That should not be a condition of approval.

One, no, it should not be a condition of approval, but somewhere the panel will have to address the fact that some patients in rare instances will need additional imaging studies, and we should address that if for nothing more to give patients leverage on their payers to support those studies.

CHAIRMAN WHALEN: Thank you.

Dr. Witten, in regards to the three questions, the panel does not collectively feel that any of these issues would need to be evaluated by the sponsor prior to consideration of approval of their application, but nevertheless, I believe there is a preponderance of concern about several of the issues, and specifically mostly centered upon that of the possible interference with mammography, and that this should be something that would need to be studied in the future.

Does that answer the question?

DR. WITTEN: Yes, thank you.

CHAIRMAN WHALEN: Thank you.

And finally, question number seven, and this, I believe, is the other one that we can be a little bit less formal about going around the table, has to do with heterogeneity of surgical practice and recommendations for what issues should be included in physician training vis-a-vis this particular device and its implantation.

Does anyone wish to comment upon that?

Ms. Dubler.

MS. DUBLER: I'm impressed by some of the discussion of the importance of surgical technique in these sorts of surgeries, and I'm also impressed by the fact that this is a growing field, and cosmetic surgery is now described as one of those fields outside of the restrictions of managed care, and therefore, lots of people are finding it attractive, and that makes me very anxious about some of the people who will be engaged in these surgeries.

And, therefore, I would expand this topic not only to address surgical training, but to also address potential patients and tell them to be aware

of the fact that surgical training varies in these areas, and it's one of the discussions they ought to have with a prospective provider.

CHAIRMAN WHALEN: Ms. Domecus.

MS. DOMECUS: I guess as a follow-on to that, I think that physician training should not just involve the surgical techniques and information about the device, but apparently information about the informed consent process.

This morning session, that was the most alarming part of all that to me, was how many of these patients didn't feel like they got adequate information or any information on the risks and benefits to make an informed decision, and so I think that the sponsor could go a long way in helping its physician customers understand what an adequate informed consent process looks like.

CHAIRMAN WHALEN: Dr. Witten, in an attempt to answer this question and perhaps even taking the purview of the chair and editorializing a little bit myself as a Program Director in general surgery, I think there is concern about what

practitioners do, and there is concern about both physician training and how much the public who is interacting with these physicians knows about such issues, but I would add myself that I don't know that there's anything that we can impose upon this or any other sponsor which is going to be a requirement vis-a-vis that particular aspect of the training.

Does that answer the question?

DR. WITTEN: Well, I do have one follow-on question, and just to see if anyone has anything to add, which is have we learned anything from the study and the information the sponsors provided that leads us or leads you all to recommending anything specific in the label regarding surgical practices and post operative management with this particular product based on the information that was provided from the studies.

CHAIRMAN WHALEN: Dr. Burkhardt?

DR. BURKHARDT: The information provided in the studies shows that you can't push one of these things through a small hole without maybe injuring it, and I would think that it would be reasonable to

suggest to the FDA that they advise against insertion through a long, small tube by way of the umbilicus.

DR. WITTEN: Thank you.

DR. CHANG: And I think that this issue of Betadine perhaps changing the integrity of the device, and particularly the length of incision, may be added in the labeling.

DR. BURKHARDT: Could I speak to that issue?

CHAIRMAN WHALEN: Dr. Burkhardt.

DR. BURKHARDT: The two major problems we have are deflation and capsular contraction. There is new evidence that is presented here that the Betadine may make deflation more common. There is evidence in the literature that it may make capsular contraction less common.

And I would suggest to you that this should not be an issue of device approval, but should be left up to the judgment of the operating surgeon.

CHAIRMAN WHALEN: I guess the only response I would have to that is ultimately it's going to be anyway, isn't it? Ultimately it is going to be

up to the surgeon, and the surgeon is going to do whatever he darn well pleases no matter who tells him anything.

Some of you probably think since we answered all seven questions that we're now going to vote. You're wrong.

(Laughter.)

CHAIRMAN WHALEN: We will now proceed with the second open public hearing session of this meeting. All those and only those who have signed up for this -- there are four people -- who will address the panel should speak clearly into the microphone as the transcriptionist is dependent upon this means of providing an accurate record of this meeting.

The instructions from this morning still apply, and to briefly encapsulate those, we would ask that you disclose if anyone is paying for your trip or accommodations; if you have any financial ties to industry or health professional societies. We would also ask that you disclose whether you are a witness or party to any lawsuits related to breast implants or whether you derive any of your income from medical

procedures involving breast implants or symptoms attributed to breast implants.

Each speaker in this session, unless there's a loud outcry, was originally going to be allotted ten minutes, and in view of the hour, the chair is going to ask that you confine that to five minutes, and we only have time for the four scheduled speakers.

The first one is Lale Goddard.

MS. GODDARD: (Inaudible.)

CHAIRMAN WHALEN: If you feel that it's so critically important, then please proceed.

I'm sorry. Just for the timer's sake then, ten minutes on this please.

MS. GODDARD: My name is Lale Goddard.

Now can you hear me better? I don't need to holler, right?

Okay. My name is Lale Goddard. Thank you very much for the opportunity to appear before you today.

I paid my own travel and accommodations. I do not have financial ties with industry or health

professional societies. I am the plaintiff to a pending lawsuit related to breast implants. I derive no income from surgical procedures.

I'm here today because scientific literature states that particulate wear debris generated from implanted medical devices may not be biocompatible. Long term implantation of various medical devices, such as breast implants and joint implants, can generate particulate wear debris.

White blood cells, called macrophages, can be stimulated or activated when they ingest silicone elastomer particles. Activated macrophages can synthesize and release various inflammatory mediators, such as the pro inflammatory cytokines called tumor necrosis factor alpha.

Tumor necrosis factor alpha induces the production of another inflammatory cytokine called interleukin-1. Tumor necrosis factor alpha and interleukin-1 are both potent and biologically active protein molecules. They act as signals between cells to regulate the immune response to injury or infection.

Biological properties of interleukin-1 suggest that its effects often mimic host response to infection, inflammation, injury or immunological challenge.

Once released into the circulation, interleukin-1 can induce systemic systems, such as fever, muscle aches, arthralgia, headache, lassitude, sleepiness, changes in metabolism, and hematological dysfunction.

Tumor necrosis factor alpha and interleukin-1 can be toxic in vivo. Inflammatory cytokines produce at the site of chronic granulomatous for a body reaction can move through the blood stream and activate cells at a distant site. There is growing evidence that the tumor necrosis factor alpha is involved in the onset of inflammatory arthritis, whereas the cartilage and bone destructive process is mainly interleukin-1 driven.

Interleukin-1 is responsible in the production of cyclooxygenase, an enzyme that helps make prostaglandins, the substance largely responsible for the pain and inflammation of arthritis. When

scientists injected the inflammatory cytokines into rabbits, the animals developed signs of inflammatory arthritis and join erosion.

Tumor necrosis factor alpha and beta are potent stimulators of bone resorption in vivo.

Orthopedic implant manufacturers and surgeons have known about the adverse cellular responses to particulate wear debris for decades, and they call it a chronic granulomatous foreign body reaction or particle disease.

Scientific literature states that silicone elastomer particles can cause erosive or destructive arthritis that mimic rheumatoid arthritis. Long term benefits of silicone elastomer use in joint implants probably far outweigh the risks of complications and adverse reactions for most orthopedic patients.

The cosmetic and psychological benefits of long term breast implants made with silicone elastomer shell in healthy women may not outweigh the possible risks and complications. The FDA recognized standards for biological evaluations of medical devices and guidance documents do not require the manufacturers to

do testing for cellular responses to silicone elastomer particles.

The particle testing could be done in less than three weeks, according to an article published in the May 1996 issue of Orthopedic Hand Surgery. The title of the article is "In Vivo Inflammatory Response to Silicone Elastomer Particulate Debris," published by Dr. Sanjiu H. Naidu and his colleagues.

The article abstract states the following: "Silastic silicone elastomer polymers, polymethylmethacrylate particles, monosodium urate particles smaller than 10 microns were injected into a rat subcutaneous air pouch lined with synovial membranelike cells. Inflammatory exudate from the air pouch was retrieved at 6 hour, 24 hours, 48 hours, and 72 hours after injection. White blood cell count, tumor necrosis factor, and prostaglandin $E_2$ were measured in the exudate. White blood cell and tumor necrosis factor levels in the exudate were the highest for the silicone group in 24 hours. Prostaglandin $E_2$ was significantly higher in the silicone group at 24 hours. We concluded that acute inflammation is

particle-type specific and that silicone elastomer particles are acutely inflammatory."

In 1998, American Society for Testing and Materials developed two particle testing standards. One is titled "Testing for Biological Responses to Particles in Vitro," and the other is titled "Standard Practice for Testing the Biological Responses to Particles in Vivo."

Both standards state the following: "it is well recognized that the biological responses to particles could be different from those to solid materials. The interaction of the particles with cells in the tissue, notably macrophages and other phagocytic cells, is the key to final biological responses."

The standards describe techniques used to detect soluble cell products, such as tumor necrosis factor alpha, interleukin-1, interleukin-1 receptor antagonist, and interleukin-6 due to interaction of phagocytic cells, such as tissue macrophages and synovial lining cells with particles.

For consumer safety sake, please consider

making the following recommendations to the FDA.

One, the FDA to recognize the American Society for Testing and Materials standards titled "Testing for Biological Response to Particles in Vitro" and the "Standard Practice for Testing the Biological Responses to Particles in Vivo."

Two, the FDA to updated and include the two particle testing standards in the guidance document.

Three, the FDA to not approve silicone inflatable breast implant manufacturers' pre-market approval application or product development protocol until the manufacturers comply with the revised guidance document.

Four, the FDA to analyze the explanted elastomer shells to determine the amount of material lost.

Five, if the FDA approves breast implant manufacturers' PMAs and PDPs without the testing for cellular responses to silicone elastomer particles, then the FDA should inform the public that the particle testing was not required for the PMA and PDP

approvals.

Please do not vote for the approval of breast implant manufacturers' PMAs and PDPs without the requirement for testing for cellular responses to silicone elastomer particles. Particles to be tested should be smaller than 13 microns or small enough to be ingested by macrophages or other phagocytic cells.

Manufacturers should inform doctors and patients about the cellular responses to silicone elastomer shell particles and cytokine production.

Thank you very much, and my written statement is also available at my Web page, jps.net/joseeefus/.

Have a good evening.

CHAIRMAN WHALEN: Thank you.

Next we will hear from Ms. Rosmary Locke on behalf of the Department of Defense Military Hospital Beneficiaries.

MS. LOCKE: Thank you.

It's been a long day, but I really do appreciate the opportunity to speak to you after one of the manufacturers presented and the FDA made the

comments.

My name is Rosmary Locke, and I have no personal financial involvement with manufacturers or health care providers. I'm not involved in a legal issue, and I'm not being reimbursed.

However, I am a volunteer for Y-ME national breast cancer organization, and it's my understanding in the past they did receive small donations from one manufacturer. The bulk of our -- that's all public record in our annual reports -- the bulk of our money comes from individual donors and some pharmaceuticals who support our work.

I am a breast cancer survivor of 15 years with implants. I'm a military spouse and a health care advocate for military beneficiaries. I'm also a past president of the National Military Family Association.

Eight years ago I was a member of your advisory panel when it reviewed the PMA on gel implants. Though I believed that gel implants were safe, I concurred with the other panelists that the scientific information was lacking for gel approval.

Since then a large body of science has emerged showing that breast implants do not cause systemic disease. The National Academy of Science's IOM review of the science, its conclusions and recommendations now provide us with knowledge based on sound science.

Saline implants are a very important option for women who face breast cancer. At diagnosis, treatment options must be considered and difficult decisions made with the hope that disease can be controlled and a more normal life resumed.

That is why it's so important to have a full array of treatment options. It gives the cancer patient some sense of control and restoring her health and quality of life.

While saline breast implants generally do not produce the desired aesthetic results of gel in reconstruction, saline offers mastectomy patients the only unrestricted option left since the FDA's restrictions in 1992.

Saline is the only implant option for breast cancer patients or long term survivors treated

in military hospitals, and access to gel for reconstruction is a problem for many women in the civilian sector.

And I know because time is limited you're probably not going to ask any questions on why that is, but it is a significant problem for military beneficiaries.

I urge this panel to stick to the science, consider the exhaustive and definitive review of the IOM of all of the existing research. The IOM found that there's no evidence that silicone breast implants cause disease or cancer. Yet the FDA restrictions on gel remain, denying access or causing delays for some women seeking them for reconstruction.

Look at the fear and the litigation that happened after the 1992 PMA on gel. FDA cannot and should not act in a vacuum.

Now, there have been many other reviews that were spoken of today, and each found similar findings to that of the IOM. The research shows no increase in primary or recurrent breast cancer. Indeed, though we've heard from a number of women who

have a wide range of medical conditions they attribute to breast implants. Their health needs cannot be ignored.

The FDA, however, cannot make regulatory decisions based on personal anecdotes. It must stick to the science.

Of course, a woman considering reconstruction should seek in depth information about her cancer and her reconstruction. Now, the National Cancer Institute, FDA, IOM, and many medical institutions have excellent information in print and Web pages, and many women find it helpful to talk to other cancer patients.

Consumers need to know that no medical device is risk free. No medical device lasts forever. And there are risks associated with all surgical procedures. That makes informed consent central to the process. It's absolutely essential for doctors to advise their patients on the risks and benefits of any medical procedure.

Though quite sobering, we welcome the information coming from the manufacturers on the

nature and frequency of complications and reoperations.

We also appreciate the opportunity by the FDA to make comments on informed consent and labeling, and we ask to be able to make a statement on that.

In summary, I ask that breast cancer treatment decisions should be made on how best to treat cancer, not on disfiguring surgery, and breast implants offer an important option to women with breast cancer.

I urge this panel to base its recommendations on sound science and studies with reasonable endpoints, a process FDA uses in evaluating all other effective medical devices and therapies.

Thank you.

I did cut my time. It may not seem like it with the red light going.

CHAIRMAN WHALEN: Thank you.

We next will hear from Dr. Diana Zuckerman from the National Center for Policy Research for Women and Families.

DR. ZUCKERMAN: Is this a good height?

Oh, towards me? Is that better?

I'll be brief if you stay awake. That's the deal.

(Laughter.)

CHAIRMAN WHALEN: Hunger is a wonderful motivator. Please continue.

DR. ZUCKERMAN: Thank you.

I just want to briefly say that I come to be here -- oh, I should start with my conflicts of interest. I'm donating my time, and my transportation here all the way from Bethesda, and my answers to the other conflict of interest questions are no.

My background is in epidemiology and psychology, and I've also talked to hundreds of women with breast implants of the last ten years, and so my goal today is to put those two things together.

I know that we as scientists are not supposed to focus on anecdotes, but sometimes when we listen to patients, it tells us something important, and when we tie that in with what the research does or doesn't tell us, I think it can be very important and give us some insights into where we go next.

I'm very concerned about the loss of patients to follow-up in the studies that you've heard about, and I'm particularly concerned about it because I've talked to a lot of implant patients who have told us, told me personally of experiences where they try to tell their doctor that they have problems.

And it isn't getting registered in the studies that they are supposed to be in, or they get so turned off by doctors who do not seem to believe that their health problems can possibly be related to their implants that they stop seeing those doctors and go find other doctors.

And so I think it is not a minor issue that there is this loss of patients to follow-up, and several of you have raised that question, and then I feel it's sort of gotten lost. It's the long day and it's the end of the day, and so I want to bring you back to that issue, that perhaps part of the reason why the women who had problems sound one way and the research seems so entirely different is because some of those women at least are getting lost.

And of course, we don't know how many

there are, and that's very important, and I think that's a big issue, certainly for me, and I hope it will be for you.

I also want to talk a little bit about the quality of the data, and that ties in again. I mean obviously a study of depression that has no comparison sample or control group, I mean it reduces the credibility of the whole package to me to have something like that be supposed to be evidence that these women are getting better because, of course, women who have just had surgery for breast cancer are going to be depressed.

I used to do research on depression. I promise you that's true. They are going to feel better, and without a comparison sample, you don't know anything about how effective this particular treatment is for those women.

I also have some concerns about whether all of the right questions were asked in these studies. Pain is a big issue for a long of the women I talk to. I'm not at all convinced that the research that was presented today really deals with pain in a

meaningful way.

Obviously if women say they're really satisfied with their implants, you have to assume that pain is not a big problem, but let's remember that the follow-up was quite short for these studies. Three years is not a very long time.

When I've talked to women, most of these women have been very happy with their implants for the first few years. It's only after three or four or five or six or more likely seven or eight years that they start having serious problems.

And let me also mention that part of that is that when they do have problems initially their doctors say, "Don't worry. It's going to get better," and so they have this hope, and they may feel quite satisfied because they think that the problems that they have of pain or numbness in the nipple area or whatever it might be, that those problems are going to go away and they're going to feel better soon.

If you follow them for a longer period of time, they might feel quite differently about how satisfied they are and how they feel about it.

Let me briefly say I'm on the Scientific Advisory Committee for the NCI study of breast implants. I was very surprised that that study wasn't mentioned here today. I Know that the data are not -- nobody knows better than me the data are not public yet.

I would have thought FDA would have asked for those data. I would have thought they would have presented those data to you. Although it's not published yet, some of those data are already analyzed, and one of the people at FDA is a co-author of those studies.

Those are studies of cancer, breast cancer and other cancers, and a study of connective tissue disease. Those are relevant data. Those are important data. It's a very large study, the largest study that's ever been done, and I don't understand why you didn't get it, and I hope that FDA will ask for it and look at those data before any kind of final decision is made.

I'm almost done here.

There's one thing I just have to address,

and that's the issue of connective tissue disease. When I was asked to speak today and all the other public comment people were told stick with saline implants, and I'm happy to do that, but the studies on connective tissue disease do not do that.

I may be one of the few people in America who's actually read all of these epidemiological studies on connective tissue disease and breast implants. Here they are. I've read all of the. I've done a review of them.

And let me tell you that of the 17 studies that are most often quoted in the Institute of Medicine report, as well as other reports that have been done, only one, one study looked at saline breast implanted women and analyzed them separately. None of the other studies did.

Most of the studies had no women with saline implants or very small numbers that were not analyzed separately. If you want to assume that the data on silicone gel implants are relevant to saline, that's a decision to make, but it's kind of an unusual decision to make. Usually you would study, you know,

one product at a time and base your decision on that one product.

Finally, I just want to say that there is a lack of long term data. I think that's serious, and I commend your concern about that and your asking for more data.

As someone who's done survey research, I don't think there's any way in the world you're going to get questionnaire data ten years out. You may say it's impossible to get, you know, actively women coming back in, but you're sure never going to get questionnaire data like that.

If you think that long term data are important -- I personally think they're very important -- I don't know how you're going to create an incentive for the manufacturer to do that if you approve these devices. If they haven't done it up till now when they had all these years to do their studies, what's going to give them the incentive to do it in the future?

And my understanding is that FDA does not have post market surveillance resources or perhaps

authority for medical devices. So if you think that the data that's been presented are not sufficient to prove safety, and I know that some of you have said that here today, then you have to think very carefully about how you're going to make sure that happens when I think there is actually no other way to make sure it happens.

And my last comment is just to say that breast cancer patients are a special case, and Dr. -- not doctor -- Ms. Dubler and I commend your concern about them, and I share it.

I've worked with a lot of breast cancer activists, and I actually met with them very recently to talk about this issue, and there's a wide range of feelings among the breast cancer community about breast implants. Most groups have been neutral on the issue. They all do want good data.

We do women no favor, whether they're breast cancer patients or any other patients, we do them no favor by leaving something on the market that is not proven safe for them.

Thank you.

CHAIRMAN WHALEN: Thank you.

Finally we have -- Dr. Zuckerman, if you'd stay at the podium, there's a question.

DR. ZUCKERMAN: Sure.

DR. BLUMENSTEIN: This NCI study, I did not know about it, and I think that it has a possible impact on what other kinds of data we require of the manufacturers, and I would like to know some more details about it.

CHAIRMAN WHALEN: Well, before you go into any details about that, Dr. Witten, would you like to comment upon the whole process we're about in terms of what PMAs are and what we can review?

DR. WITTEN: Yeah. I just want to reiterate what I had mentioned this morning, which is we want you to base your safety and effectiveness assessments on the information contained in the PMAs, and in addition, your scientific knowledge, including, you know, what you know from publicly available scientific literature.

CHAIRMAN WHALEN: Which is what we are mandatorily directed to do.

DR. WITTEN: Which is what we're directed to do.

DR. ZUCKERMAN: No, and I understand that, but I have heard people say, "We don't have to worry about cancer or connective tissue disease because the studies show there are no problems," and I am not at liberty to say what's in those studies even though I have seen them. I am not allowed to talk about them.

I'm only saying I think that that would be something that FDA would want you all to look at and would want to look at.

CHAIRMAN WHALEN: Thank you.

Finally, we have Ms. Jill McClure from the National Alliance of Breast Cancer Organizations.

MS. McCLURE: Good evening. Thank you for your time.

My name is Jill McClure. I'm a health educator and a breast cancer information specialist. It's my pleasure to represent the consumer and professional constituencies of the National Alliance of Breast Cancer Organizations and to offer a point of view to the members of the panel.

My travel expenses have been paid for by internal NABCO funds earmarked for advocacy activities. Neither NABCO nor I have any financial ties to implant manufacturers or marketers. NABCO does not receive any funding from any current implant manufacturers. Neither NABCO nor I are part to any implant related lawsuits.

The reason I phrased it current implant manufacturers, I know, for example, Bristol was an implant manufacturer, and they're somebody who has supported a publication of ours this year. So I want to be absolutely clear on that.

I would like to emphasize that my remarks will be confined to use of these devices for reconstruction for women who have had breast cancer or breast disease or who have had a prophylactic mastectomy due to an established risk for breast cancer.

NABCO cannot and does not comment on the cosmetic use of breast implants of any type.

NABCO is a not for profit, information and education resource on breast cancer. It is also a

network of over 400 member organizations and a nationally recognized voice for the needs and concerns of women with breast cancer, women at increased risk for the disease, and their friends and family.

NABCO's professional staff members are frequently called upon by providers and health professionals to serve as patient advocates and advisors in medical and policy deliberations and in clinical decision making.

We also frequently translate scientific developments and advances into understandable and compelling language for print and broadcast media.

We're comfortable taking on these roles and responsibilities because NABCO's mission and program areas offer us constant exposure to a large and varied constituency.

I work in NABCO's Information Services Department where our Web site and toll free number are NABCO's front line for serving the public and where we handle hundreds of weekly contacts with many segments of patient and survivor communities.

Callers express their breast cancer and

educational needs, and as we fulfill those needs with materials, resources, and referrals, we've often heard misinformation, confusion, and concern, but also some reassurance and relief surrounding the emotionally volatile subject of breast implants.

Without question, saline implants are not ideal since they can leak, be subject to capsulary contracture, and are less sturdy, require higher maintenance, and are often less aesthetically acceptable than their silicone filled counterparts.

We at NABCO hope and expect that the FDA will address the availability of silicone filled breast implants, again, for breast cancer patients and survivors at some point later this year, but until these devices are open for discussion, we wish to make several points about saline breast filled implants.

Safe, well tested, saline filled breast implants must continue to be available in as many types and forms as feasible so that options and choices for women with breast cancer are maximized. The alternatives of autologous tissue reconstruction and external prosthesis are not appropriate for every

woman, and as individuals differ and vary, so much their options.

Like any medical device or procedure, saline breast implants should be considered and selected by a woman and her medical team after careful discussion and consideration with a full information exchange that includes the risks and benefits.

Saline filled implants have been available and, as such, have not been subject to the more stringent and highly regulated informed consent provisions and requirements of clinical trials.

However, there still remains confusion about implants, and for this reason NABCO calls upon the device manufacturers and the medical specialists and providers who use these implants to make special additional efforts.

Women who are considering saline implants should receive an exceptionally thorough, comprehensive, and understandable information review about the devices from their physicians, be given time to ask questions and have those questions answered.

Information conveyed should not only

include what to expect when the saline implants are first received, but how the devices will behave over time both under normal circumstances and under unusual circumstances.

NABCO encourages giving women contact information for organizations that can offer accurate and balanced information about implants and breast health in general. Understanding and working with her implant is a woman's lifelong commitment and part of the decision to choose an implant.

It should be made clear that replacement of a saline implant is not only possible, but likely, and the woman shares the responsibility with her physician for keeping up with developments about implant improvements, advances, safety, and this idea of maintenance.

Women with saline implants need to know the special considerations and requirements for breast examinations for early detection of breast cancer. MQSA regulations have specified certain procedures for imaging women with implants, and these must be taken into account at the time a woman has an implant in

place or -- I'm sorry -- and the type of implant the woman has in place.

Breast self-examination techniques should be reviewed with the woman after the implant has resolved to its ultimate size and resting place. The breast cancer survivor should be particularly vigilant about breast examinations and the possibility of recurrence.

Finally, NABCO urges the FDA to move forward with communication of scientific findings about breast implants, and that all types of these devices be discussed using factual scientific and evidence based information rather than relying on or giving consideration to emotional, personal, and anecdotal experiences.

Women who have survived breast cancer are particularly able to weigh the risks and benefits, understand that no medical intervention is risk free. Having become informed patients by selecting the treatments that would extend their lives, patients and survivors need and deserve similar choices even if they seem difficult or challenging, including breast

implants and any other regulated aspect of recovery that may improve the quality of their lives.

As their advocates, we have confidence that these women will make wise choices that are right for each one of them based on full disclosure.

Thank you for your time.

CHAIRMAN WHALEN: Thank you.

I'd like to thank all of those for taking time out of their schedules to testify at this panel meeting.

Is there any further comment from anyone in the FDA?

DR. WITTEN: No, thank you.

CHAIRMAN WHALEN: Thank you, Dr. Witten.

Will there be any further comment from Mentor Corporation?

Seeing that there will be, I'd like to remind you beforehand that this will be for ten minutes. I would ask that the timer be run to that accord, and also remind you that this is not to present new data, but just to comment upon anything that has already taken place.

MR. PURKAIT: Thank you, Mr. Chairman.

Thank you, members of the panel, for your time and the thoughtfulness and seriousness that you have shown to consider our PMA today.

There are some issues that I saw or we saw here you panel members are struggling about the data, specifically on the complication rates. I'll take only a few seconds or minutes jut to show that some of this data that we presented did not show the complication rates increasing over time.

I'd like to call these slides here, please.

This is from the augmentation patients. I wouldn't take much time to explain each of those data. I just want to draw your attention to the fact that the year one, year two, year three, you can see the year one they are higher, as it goes down in year two and year three. All categories go down except the reoperation, what we have explained before.

Slide number two please.

Similarly on the hematoma, seroma, necrosis breast pin, and the others, what we have

calculated through the Kaplan-Meier, which we have submitted also, that shows that the year one, year two, year three decreasing, not increasing.

Similarly, on the reconstruction patient, please. On the reconstruction patients, I'd like to also point out that infection goes high at the year first and goes decreasing rate over two and three. Similarly on the deflation, deflation probably is in the higher scale, which we have explained the reason behind it. Reoperation rate and explantation goes high in case of the reconstruction.

Similarly, in the other areas of complication, the hematoma, necrosis, seroma, all of them shows higher rate at the year one, year two, and year threes on the decreasing.

This one, the extrusions and the rest of the other complications, this is an example to show that what you're struggling before about the safety issues related to the fact that this goes over -- increase over time. I like to present this to keep the record straight that this doesn't really.

The second thing that I'd like to mention

is that in case of the division patients I request strongly to the panel members to consider this carefully because the division patient groups are in between, and I do not like to see that division patient groups have a cloud over their head that they can get an implant one time, but the next time they can't because there is some problem with the devices.

Also I'd like to mention that out SPS study is quite full of data, we believe rich, and has a lot of new information that we recently uncovered and discovered, and we are understanding, and we believe that as those data are being disseminated and been shared with both physician and FDA, it will be provided in the patient as well as the physician-patient information in such a way that we'll be able to provide a better information than before, previously, to the whole community.

With those notes, again, I thank you very much for your consideration, and I believe that this will give you a pretty good idea about our PMA's data and will help you to understand this data and vote on it.

Thanks.

CHAIRMAN WHALEN: Thank you.

Dr. Krause will now read the voting instructions for the panel.

DR. KRAUSE: Thank you, Dr. Whalen.

I'd now like to read the voting instructions for the panel.

The medical device amendments to the Federal Food, Drug, and Cosmetic Act as amended by the Safe Medical Devices Act of 1990 allows the Food and Drug Administration to obtain a recommendation from an expert advisory panel on designated medical device pre-market approval applications that are filed with the agency.

The PMA must stand on its own merits, and your recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information.

Safety is defined in the act as reasonable assurance based on valid scientific evidence that the probable benefits to health under conditions on intended use outweigh any probable risks.

Effectiveness is defined as reasonable assurance that in a significant portion of the population the use of the device for its intended uses and conditions of use, when labeled, will provide clinically significant results.

Your recommendation options for the vote are as follows.

First option: approval if there are no conditions attached.

Second option: approvable with conditions. The panel may recommend that the PMA be found approvable subject to specified conditions, such as physician or patient education, labeling changes or a future analysis of existing data. Prior to voting all of the conditions should be discussed by the panel.

Third option: not approvable. The panel may recommend that the PMA is not approvable if the data do not provide a reasonable assurance that the device is safe or if a reasonable assurance has not been given that the device is effective under the conditions of use prescribed, recommended, or

suggested in the proposed labeling.

Following the voting, the chair will ask each panel member to present a brief statement outlining the reasons for their vote.

CHAIRMAN WHALEN: Thank you, Dr. Krause.

Does one of the panel members wish to make a motion?

DR. BURKHARDT: Yes, Mr. Chairman. I move that the panel recommends approvable with conditions for this PMA, and that those conditions should include post approval studies specifically consisting of some of the mechanical in vitro engineering concerns that have been expressed by Dr. Li.

In addition, I would attach labeling revision concerns, specifically including a revision of the comments regarding the shaped implant and labeling to discourage periumbilical insertion.

CHAIRMAN WHALEN: As to the motion that there be a recommendation that this be approvable with conditions -- and we will discuss those conditions shortly -- but as to that motion, is there a second to the motion?

DR. LI: Second.

CHAIRMAN WHALEN: We will now consider each of the conditions which have been stipulated by the motion, and if you could once again please read for us, Dr. Burkhardt, or refresh for us what the first stipulation would be.

DR. BURKHARDT: The first stipulation was that additional mechanical testing be performed in cooperation with the FDA to address some of the concerns that have been raised.

CHAIRMAN WHALEN: Thank you.

Is there any discussion of that stipulation? Dr. Li.

DR. LI: Do you want specific suggestions? Is that where we are?

CHAIRMAN WHALEN: Well, just in support of that being a condition or not.

DR. LI: Yes.

CHAIRMAN WHALEN: Or amplifying or --

DR. LI: I'm obviously fully in support of that. Is that all you want now or do you want the actual conditions for approval?

CHAIRMAN WHALEN: I'm not trying to be a ventriloquist. You can either talk about it as much as you wish or just say you approve it and leave it there.

DR. LI: Oh. Well, I would approve it with -- surprisingly, I would actually approve it with conditions perhaps. I think minimally you need to complete the testing of all the models that you intend to sell, and I think it's important that you test them with the materials that you intend to sell in the sterilization conditions in which you sterilize them at.

So if you're going to consider gamma sterilization as a potential fall-back manufacturing process, I think it is imperative that you test it in those conditions.

Further, we didn't mention it before, but gamma sterilization raises the whole issue of shelf aging and things like that, which are probably much less important for dry heat.

I think there needs to be either a modification or perhaps even just a further